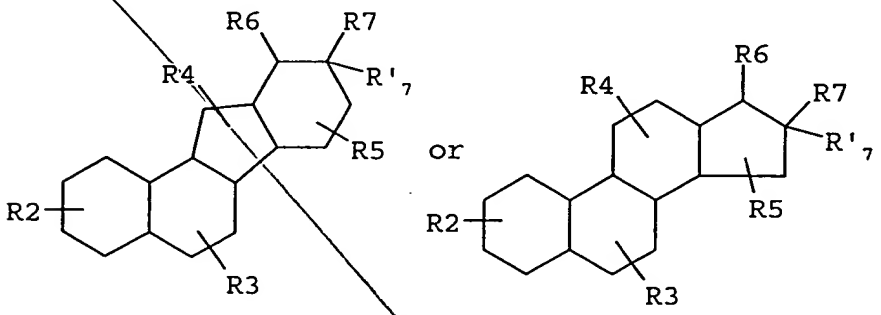
Claims

1. A method for inhibiting paracrine and/or autocrine signals produced by a hedgehog proteins comprising contacting a cell senstive to the hedgehog protein with a hedgehog antagonist in a sufficient amount to reduce the sensitivity of the cell to the hedgehog protein, wherein the hedgehog antagonist is a organic molecule having a molecule weight less than 750 amu.

2. A method for inhibiting an altered growth state of a cell having a ptc loss-of-function phenotype or a smoothened gain-of-function phenotype, comprising contacting the cell with a *ptc* agonist in a sufficient amount to inhibit the altered growth state, wherein the *ptc* agonist is a organic molecule having a molecule weight less than 750 amu.

3. The method of claim 1 or 2, wherein hedgehog antagosit is a the steroidal alkaloid represented in the general forumlas (I), or unsaturated forms thereof and/or seco-, nor- or homo-derivatives thereof:



Formula I

wherein, as valence and stability permit,

R_2, R_3, R_4, and R_5, represent one or more substitutions to the ring to which each is attached, for each occurrence, independently represent hydrogen, halogens, alkyls, alkenyls, alkynyls, aryls, hydroxyl, =O, =S, alkoxyl, silyloxy, amino, nitro, thiol, amines, imines, amides, phosphoryls, phosphonates, phosphines, carbonyls, carboxyls, carboxamides, anhydrides, silyls, ethers, thioethers, alkylsulfonyls, arylsulfonyls, selenoethers, ketones, aldehydes, esters, or $-(CH_2)_m-R_8$;

R_6, R_7, and R'_7, are absent or represent, independently, halogens, alkyls, alkenyls, alkynyls, aryls, hydroxyl, =O, =S, alkoxyl, silyloxy, amino, nitro, thiol, amines, imines, amides, phosphoryls, phosphonates, phosphines, carbonyls, carboxyls, carboxamides, anhydrides, silyls, ethers, thioethers, alkylsulfonyls, arylsulfonyls, selenoethers, ketones, aldehydes, esters, or $-(CH_2)_m-R_8$, or

R_6 and R_7, or R_7 and R'_7, taken together form a ring or polycyclic ring, e.g., which is susbstituted or unsubstituted,

with the proviso that at least one of R_6, R_7, or R'_7 is present and includes a primary or secondary amine;

R_8 represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle, or a polycycle; and

m is an integer in the range 0 to 8 inclusive.

4. The method of claim 3, wherein:

R_2 and R_3, for each occurrence, is an -OH, alkyl, -O-alkyl, -C(O)-alkyl, or -C(O)-R_8;

R_4, for each occurrence, is an absent, or represents -OH, =O, alkyl, -O-alkyl, -C(O)-alkyl, or -C(O)-R_8;

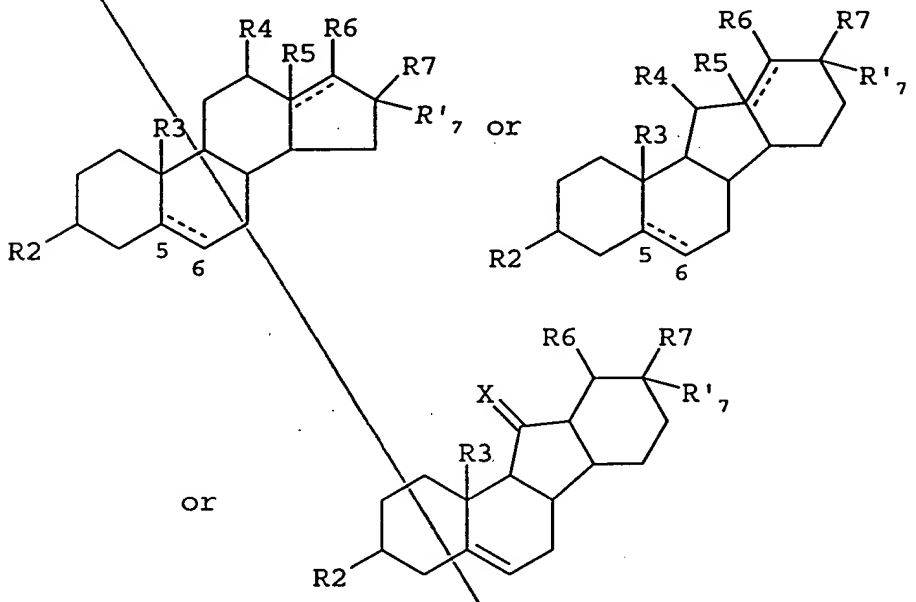
R_6, R_7, and R'_7 each independently represent, hydrogen, alkyls, alkenyls, alkynyls, amines, imines, amides, carbonyls, carboxyls, carboxamides, ethers, thioethers, esters, or $-(CH_2)_m-R_8$, or

R_7, and R'_7 taken together form a furanopiperidine, such as perhydrofuro[3,2-b]pyridine, a pyranopiperidine, a quinoline, an indole, a pyranopyrrole, a naphthyridine, a thiofuranopiperidine, or a thiopyranopiperidine

with the proviso that at least one of R_6, R_7, or R'_7 is present and includes a primary or secondary amine;

R_8 represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle, or a polycycle, and preferably R_8 is a piperidine, pyrimidine, morpholine, thiomorpholine, pyridazine,

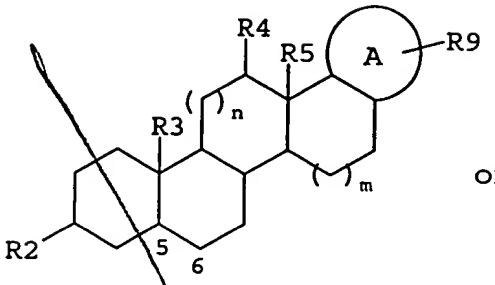
5. The method of claim 1 or 2, wherein the hedgehog antagonist is a steroidal alkaloid represented in the general formula (II), or unsaturated forms thereof and/or seco-, nor- or homo-derivatives thereof:



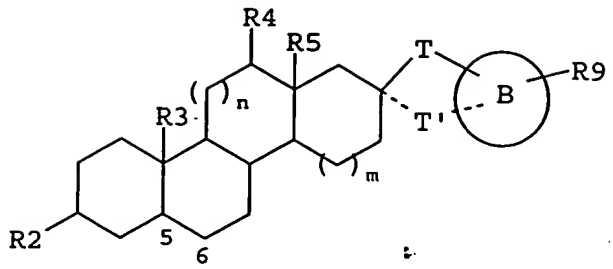
Formula II

wherein R_2, R_3, R_4, R_5, R_6, R_7, and R'_7 are as defined above, and X represents O or S, though preferably O.

6. The method of claim 1 or 2, wherein the steroidal hedgehog antagonist is a alkaloid represented in the general formula (III), or unsaturated forms thereof and/or seco-, nor- or homo-derivatives thereof:



or



Formula III

wherein

R_2, R_3, R_4, R_5 and R_8 are as defined above;

A and B represent monocyclic or polycyclic groups;

T represent an alkyl, an aminoalkyl, a carboxyl, an ester, an amide, ether or amine linkage of 1-10 bond lengths;

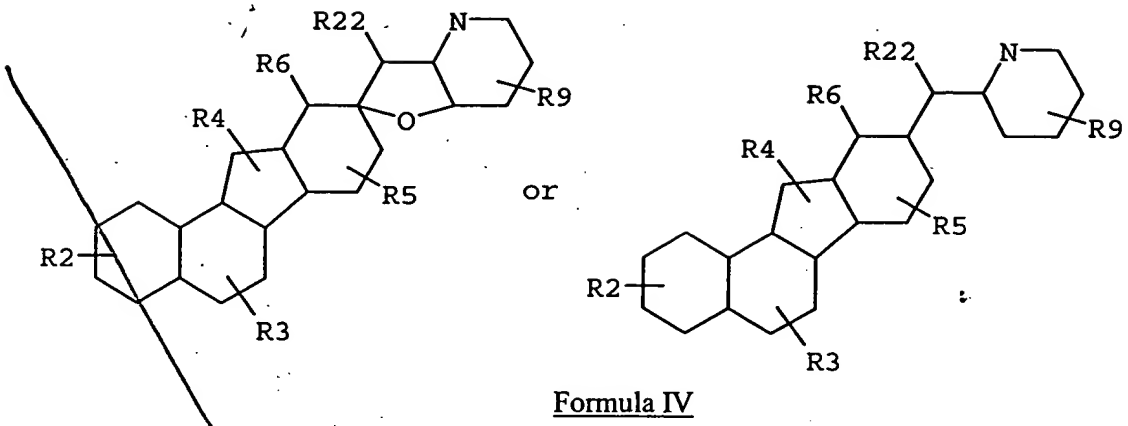
T' is absent, or represents an alkyl, an aminoalkyl, a carboxyl, an ester, an amide, ether or amine linkage of 1-3 bond lengths, wherein if T and T' are present together, than T and T' taken together with the ring A or B form a covelently closed ring of 5-8 ring atoms;

R9 represent one or more substitutions to the ring A or B, which for each occurrence, independently represent halogens, alkyls, alkenyls, alkynyls, aryls, hydroxyl, =O, =S, alkoxyl, silyloxy, amino, nitro, thiol, amines, imines, amides, phosphoryls, phosphonates, phosphines, carbonyls, carboxyls, carboxamides, anhydrides, silyls, ethers, thioethers, alkylsulfonyls, arylsulfonyls, selenoethers, ketones, aldehydes, esters, or $-(CH_2)_m-R_8$; and

n and m are, independently, zero, 1 or 2;

with the proviso that A and R_9, or T, T' B and R_9, taken together include at least one primary or secondary amine.

7. The method of claim 1 or 2, wherein the hedgehog antagonist is a steroidal alkaloid represented in the general formula (IV), or unsaturated forms thereof and/or seco-, nor- or homo-derivatives thereof:



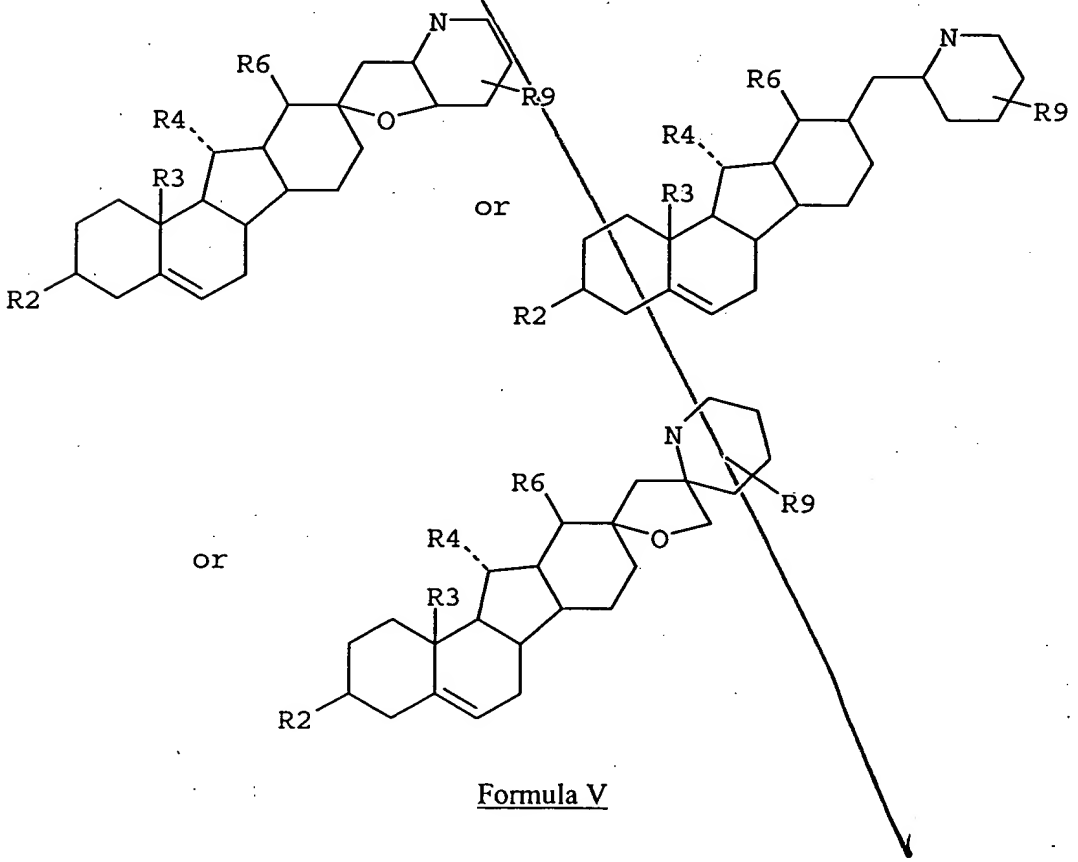
Formula IV

wherein

R_2, R_3, R_4, R_5, R_6 and R_9 are as defined above;

R_{22} is absent or represents an alkyl, an alkoxyl or -OH.

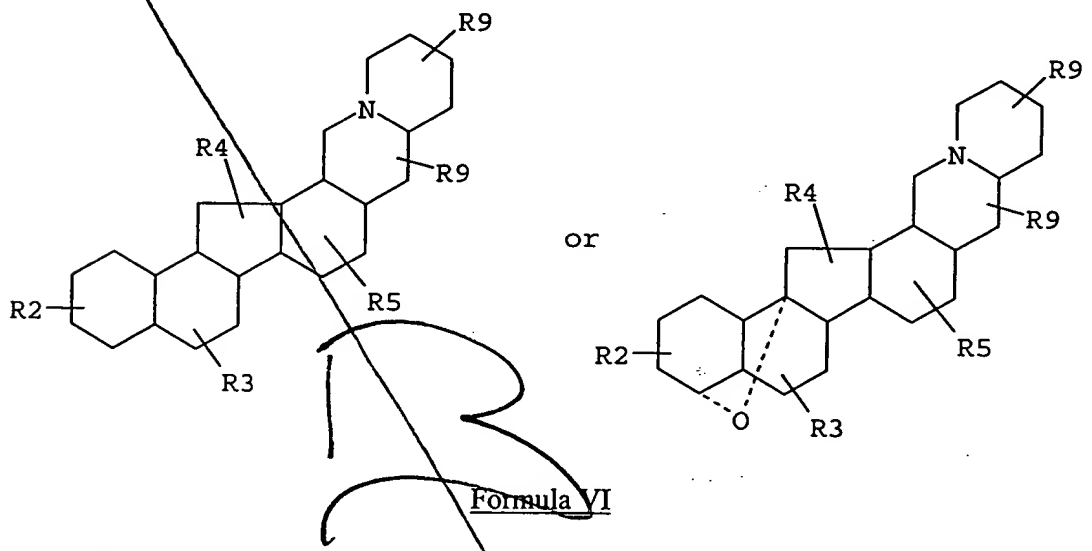
8. The method of claim 1 or 2, wherein the hedgehog antagonist is a steroidal alkaloid represented in the general formula (V) or unsaturated forms thereof and/or seco-, nor- or homo-derivatives thereof:



Formula V

wherein R_2, R_3, R_4, R_6 and R_9 are as defined above;

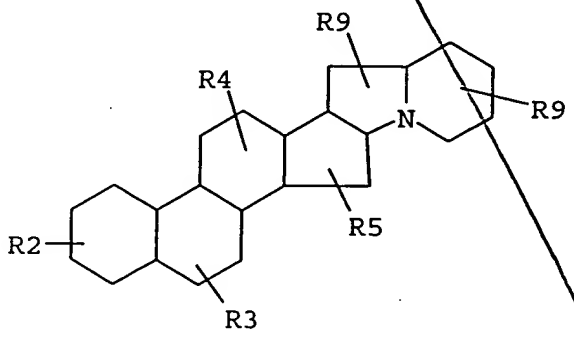
9. The method of claim 1 or 2, wherein the hedgehog antagonist is a steroidal alkaloid represented in the general formula (VI), or unsaturated forms thereof and/or seco-, nor- or homo-derivatives thereof:



Formula VI

wherein R_2, R_3, R_4, R_5 and R_9 are as defined above;

10. The method of claim 1 or 2, wherein the hedgehog antagonist is a steroidal alkaloid represented in the general formula (VII) or unsaturated forms thereof and/or seco-, nor- or homo-derivatives thereof:



Formula VII

wherein R_2, R_3, R_4, R_5 and R_9 are as defined above.

11. The method of any of claims 3-10, wherein the steroidal alkaloid does not substantially interfere with the biological activity of such steroids as aldosterone, androstane, androstene, androstenedione, androsterone, cholecalciferol, cholestane, cholic acid, corticosterone, cortisol, cortisol acetate, cortisone, cortisone acetate, deoxycorticosterone, digitoxigenin, ergocalciferol, ergosterol, estradiol-17-α, estradiol-17-β, estriol, estrane, estrone, hydrocortisone, lanosterol, lithocholic acid, mestranol, β-methasone, prednisone, pregnane, pregnenolone, progesterone, spironolactone, testosterone, triamcinolone and their derivatives.

12. The method of any of claims 3-10, wherein the steroidal alkaloid does not specifically bind a nuclear hormone receptor.

13. The method of any of claims 3-10, wherein the steroidal alkaloid does not specfically bind estrogen or testerone receptors.

14. The method of any of claims 3-10, wherein the steroidal alkaloid has no estrogenic activity at therapeutic concentrations.

15. The method of any of claims 1-10, wherein the hedgehog antagonist inhibits hedgehog-mediated signal transduction with an ED_{50} of 1mM or less.

16. The method of any of claims 1-10, wherein the hedgehog antagonist inhibits hedgehog-mediated signal transduction with an ED_{50} of 1μM or less.

17. The method of any of claims 1-10, wherein the steroidal alkaloid inhibit hedgehog-mediated signal transduction with an ED_{50} of 1nM or less.

18. The method of claims 1 or 2, wherein the cell is contacted with the hedgehog antagonist *in vitro*.

19. The method of claims 1 or 2, wherein the cell is contacted with the hedgehog antagonist *in vivo*.

20. The method of claim 1 or 2, wherein the hedgehog antagonist is administered as part of a therapeutic or cosmetic application.

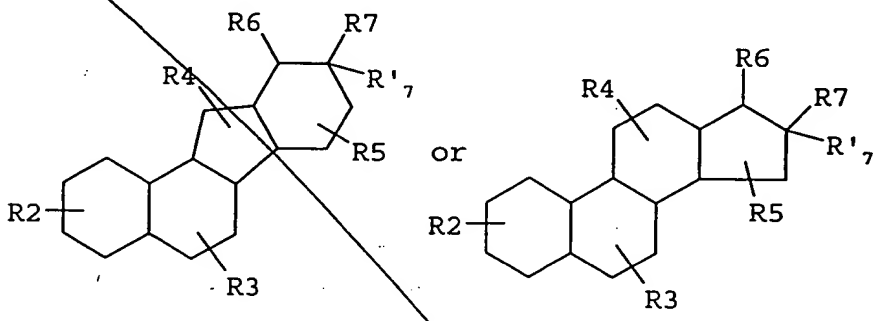
21. The method of claim 19 or 20, wherein the hedgehog antagonist is administered to treat a condition selected from the group consisting of regulation of neural tissues,

bone and cartilage formation and repair, regulation of spermatogenesis, regulation of smooth muscle, regulation of lung, liver and other organs arising from the primative gut, regulation of hematopoietic function, regulation of skin and hair growth, etc.

22. The method of any of claims 1-7, wherein the hedgehog antagonist is applied as a topical formulation to skin in order to inhibit aberrant proliferation of epithelial cells.

23. The method of any of claims 1-17 or 22, wherein the hedgehog antagonist is administered to patient to inhibit growth of a basal cell carcinoma.

24. A pharmaceutical preparation comprising steroidal alkaloid is represented in the general forumlas (I), or unsaturated forms thereof and/or seco-, nor- or homo-derivatives thereof:



Formula I

wherein, as valence and stability permit,

R_2, R_3, R_4, and R_5, represent one or more substitutions to the ring to which each is attached, for each occurrence, independently represent hydrogen, halogens, alkyls, alkenyls, alkynyls, aryls, hydroxyl, =O, =S, alkoxyl, silyloxy, amino, nitro, thiol, amines, imines, amides, phosphoryls, phosphonates, phosphines, carbonyls, carboxyls, carboxamides, anhydrides, silyls, ethers, thioethers, alkylsulfonyls, arylsulfonyls, selenoethers, ketones, aldehydes, esters, or $-(CH_2)_m-R_8$;

R_6, R_7, and R'_7, are absent or represent, independently, halogens, alkyls, alkenyls, alkynyls, aryls, hydroxyl, =O, =S, alkoxyl, silyloxy, amino, nitro, thiol,

amines, imines, amides, phosphoryls, phosphonates, phosphines, carbonyls, carboxyls, carboxamides, anhydrides, silyls, ethers, thioethers, alkylsulfonyls, arylsulfonyls, selenoethers, ketones, aldehydes, esters, or $-(CH_2)_m-R_8$, or

R_6 and R_7, or R_7 and R'_7, taken together form a ring or polycyclic ring, e.g., which is susbstituted or unsubstituted,

with the proviso that at least one of R_6, R_7, or R'_7 is present and includes a primary or secondary amine;

R_8 represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle, or a polycycle; and

m is an integer in the range 0 to 8 inclusive.

25. The preparation of claim 24, formulated for topical application.

26. A process for manufacturing a medicament comprising formulating a steroid alkaloid inhibitor of a hedgehog signal transduction pathway in a pharmaceutically acceptable excipient to from a sterile medicament for preventing growth of cells having an aberrant activation hedgehog pathway.